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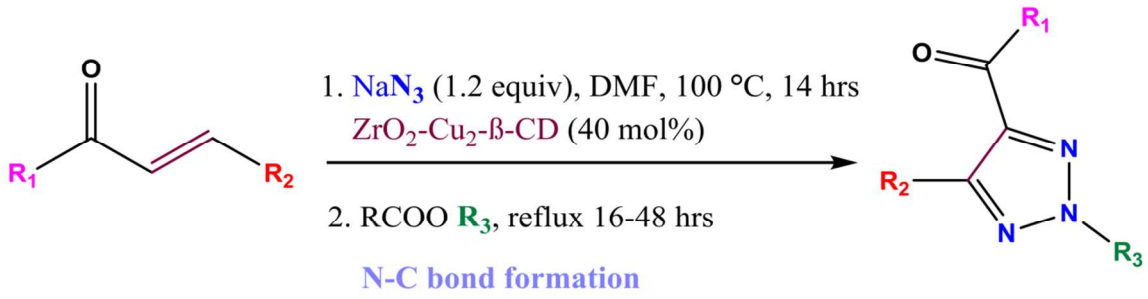

ZrO_2-Cu_2-β-CD complex is an excellent catalyst for the synthesis of N-2-alkylated-1, 2, 3-triazoles using esters as an alkylating agent.

ZrO_2 -supported Cu (II) - β-cyclodextrin complex: Construction of 2, 4, 5-trisubstituted -1, 2, 3-triazoles via Azide-chalcone oxidative Cycloaddition and Post-Triazole Alkylation

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Abstract

An efficient one-pot three-component stepwise approach for the synthesis of N-2-substituted-1, 2, 3-triazoles from chalcones, sodium azide and esters has been developed using recoverable and reusable ZrO_2 nanoparticle-supported Cu (II)-β-cyclodextrin complex as a catalyst. N-2 alkylation of triazoles using different aryl-alkyl esters without any additives has been achieved for the first time. One-pot operation, atom-economical, regioselectivity and good yields are the noteworthy features of this protocol. The reusability of the prepared nanocatalyst was successfully examined four times without any appreciable loss in catalytic activity.

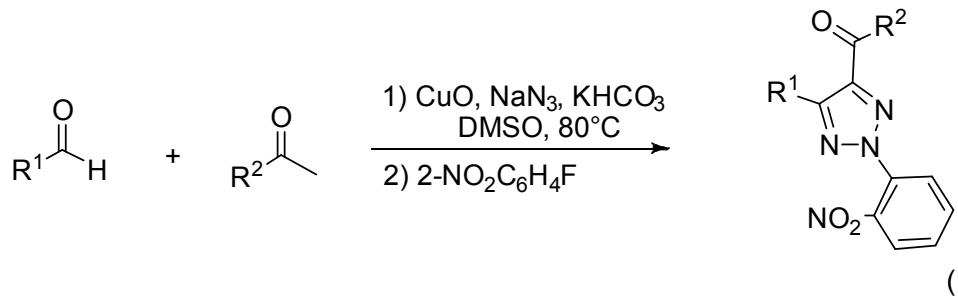
Keywords: Alkylation, Cycloaddition, N-2-substituted-1, 2, 3-triazoles, Regioselective, ZrO_2-Cu_2-β-CD.

Introduction

During the last few decennary, a great attention has been given to click[1] and green chemistry[2] for the development of efficient, ecofriendly and environmentally benign protocols. Recently nano-particles in catalysis have emerged as a sustainable and competitive alternative to conventional catalysis. In specific, nanoparticles supported on a metal oxide have been extensively studied in the field of medicine for drug delivery systems[3] and for detection of cancer cells in early stages.[4] Mesoporous nano-materials have also gained increasing importance in their use as catalyst in various organic reactions,[5,6] as sensors for detection of hydrazine,[7] optoelectronic,[8] enhancing the up-conversion luminescence,[9] and electron transfer mediator in a bio-electrochemical system.[10] The properties of metal oxide nanoparticles are very attractive compared to bulk catalysts due to their high surface to volume ratio and their surface atoms are more active and have attracted much attention because of wide spread applications in the field of science and technology.[11]

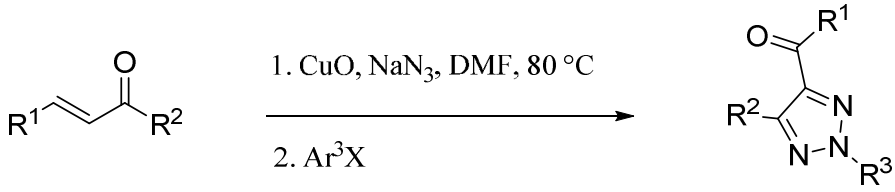
On the other hand, 1, 2, 3-triazoles are important class of five membered nitrogen containing heterocycles which have wide spread applications in various fields including organic synthesis, pharmaceutical agents, agrochemicals, dyes, corrosion-inhibitors, photo stabilizers and photographic materials.[12] 1,3-dipolar cycloaddition of organic azides with alkynes via Huisgen method is the most common approach for the synthesis of triazoles.[13] However, the above said method suffers from serious drawbacks such as high temperature, low yields and low regioselectivity. In recent years, several research groups have reported a one-pot protocol for the synthesis of 1, 2, 3-triazoles using various copper catalysts,[14] but the existing synthetic methodologies have been mainly focused on the N-1 substituted 1, 2, 3-triazoles.[15]

Previous work:



(1)[18]

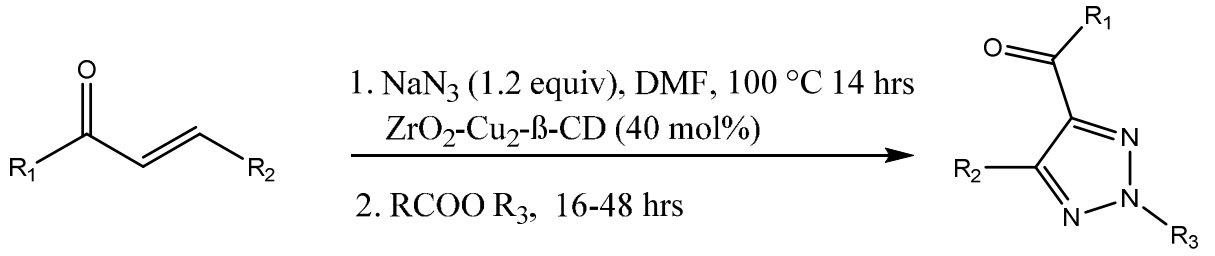
(2) [19]



(3) [20]

Chen's group of Synthesis of N-2-Substituted 1,2,3-Triazoles

Present work



1 **2**

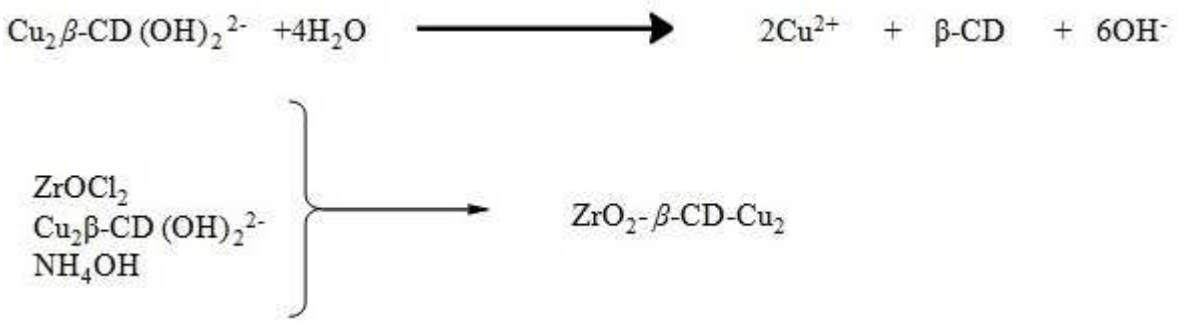
17 examples
Yield upto 82%

Scheme 1 N-2-substituted-1, 2, 3-triazole in the presence of ZrO_2-Cu_2-β-CD.

Only few methods have been reported for N-2 substituted 1, 2, 3-triazoles.[16] Generally, synthesis of N-2-substituted 1, 2, 3-triazole is achieved from hydroxy ketones and hydrazine,[17] but synthesis of α-hydroxy ketone is a challenging task. In addition, several research groups have showed different approaches for the synthesis of N-2-substituted 1,2,3-triazoles.[18-23] Most of the reported methods suffers from serious drawbacks such as limited substrate scope, high temperature, long duration, using toxic reagents and non-economical chemicals like $PdCl_2$. It is noteworthy to mention that, none of the above mentioned literature methods have used esters as an alkylating agent. Therefore, development of an efficient and safe protocol for the synthesis of N-2-substituted triazoles is still in demand. In this direction, for the first time we have developed a one-pot protocol for the regeioselective synthesis of 2,4,5-trisubstituted-1,2,3-triazoles via 1,3-dipolar cycloaddition using novel ZrO_2 nanoparticles supported Cu (II) - β-cyclodextrin complex (without any additives) followed by alkylation using esters as an alkylating agent in DMF at 100°C (Scheme 1, Equation (4)). The main advantages of this protocol are simple starting materials, one pot operation, easy workup procedure and high regioselectivity.

Results and discussion

The ZrO_2 nanoparticles supported Cu (II)-β-cyclodextrin complex (ZrO_2-Cu_2-β-CD) was prepared by a simple one-pot co-precipitation method by using $ZrOCl_2.8H_2O$, NH_4OH and the Cu (II)-β-cyclodextrin complex (Scheme 2).[24]



Scheme 2 Preparation of ZrO_2-supported Cu (II)-β-cyclodextrin complex catalyst.

The XRD analysis of ZrO_2 and ZrO_2- nanoparticles supported Cu (II)-β-cyclodextrin complex indicate five characteristic peaks at 2θ = 30.2°, 35.15°, 50.44°, 60.14°, and 62.98° corresponding to (111), (200), (220), (311), and (331) planes, respectively as shown in Fig. 1. All diffraction peaks and positions match with those from the JCPDS card (Joint Committee on Powder Diffraction Standards no. 37-1484) was calculated from the Scherer's equation,

$$d = \frac{0.9\lambda}{\beta \cos\theta}$$

where d is the average grain size of the crystallites, λ the incident wavelength, θ, the Bragg angle and β the diffracted full-width at half-maximum (FWHM) in radians caused by the crystallites. The values provided by the above equation for the ZrO_2 and ZrO_2- Cu (II)-β-CD nanoparticles were 20 and 1.6 nm, respectively. This reveals that the Cu (II)-β-cyclodextrin plays a surfactant role, which assists in reducing the size of the nanoparticles.

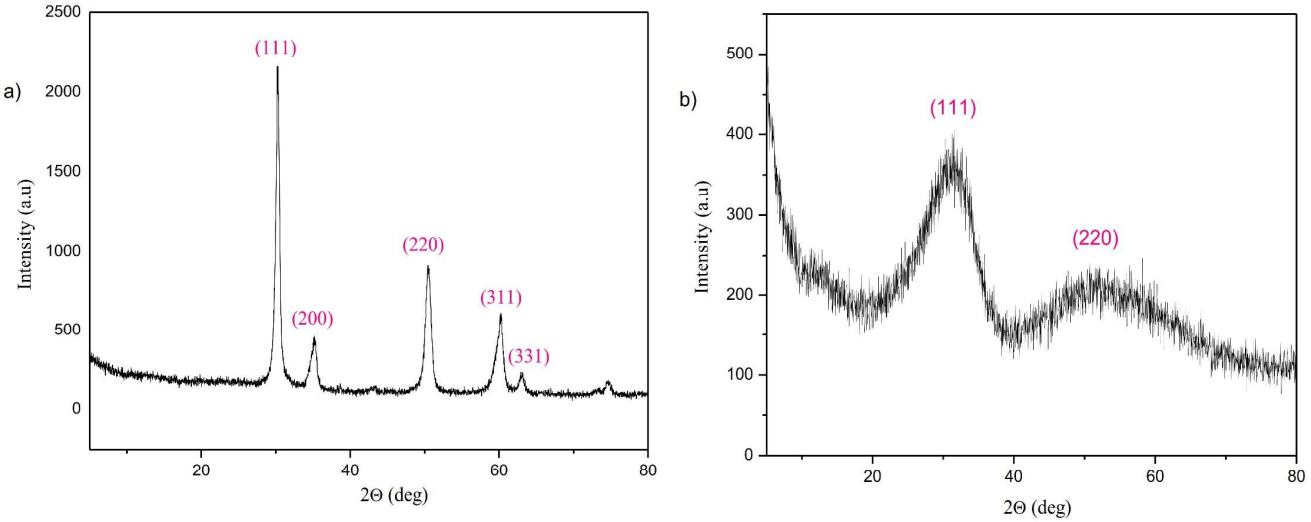
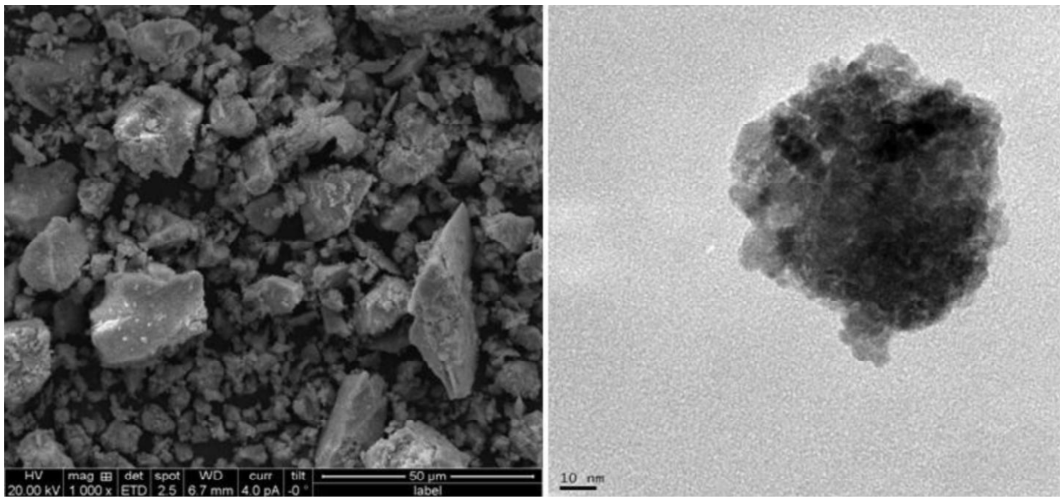


Fig. 1 (a) XRD pattern of the ZrO_2. (b) XRD pattern of the ZrO_2-supported Cu (II)-β cyclodextrin.

The SEM and TEM of the prepared ZrO_2-Cu_2-β-CD nanoparticles of ZrO_2-supported Cu (II)-cyclodextrin complex was shown in Fig. 2. The TEM image of the catalyst shows that nano particles are highly aggregated. The average size of these particles is about 1.2 nm, which shows a close agreement with the values calculated by XRD data. The SEM image of the supported catalyst confirms that these nanoparticles are uneven-sized particles due to deposition of Cu (II)-β-cyclodextrin complex nanoparticles on the surface of ZrO_2 and most of them are almost spherical in shape.



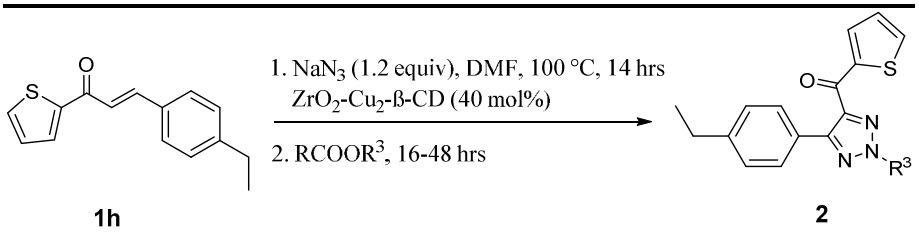
a) b)

Fig. 2 (a) SEM and (b) TEM of ZrO_2-supported Cu (II)-β-cyclodextrin.

The catalytic activity of the ZrO_2-Cu_2-β-CD nanoparticles was studied for the synthesis of 1, 2, 3-triazoles from chalcones. We initiated our studies with (E)-3-(4-ethylphenyl)-1-(thiophen-2-yl) prop-2-en-1-one (1h) as a representative substrate. Treatment of **1h** and sodium azide with 40 mol% of ZrO_2-Cu_2-β-CD nanoparticles in DMF at 100 °C produced triazole anion, subsequent addition of 2-NO_2-1, 4-difluoro benzene afforded N-2 arylated product in trace amount. Furthermore we have carried out the reaction for N-2 substitution using different aryl halides like 1, 4-dibromo and 1, 4-dichloro benzenes, in both the cases we ended up with trace amount of N-

2 arylated product. Then, accidentally we have used 2-Bromo-methyl benzoate for N-2-aryl substitution, the product spot was prominent in TLC; surprisingly the spectral analysis of the product confirms the N-methylated compound instead of corresponding N-arylated product. Inspiring by this finding, we have elaborated to different esters for alkylation. We found exclusively N-alkylated product in all the cases without any traces of N-arylated products (Table 1, entries 1-7).

Table 1 N-alkylation using different esters



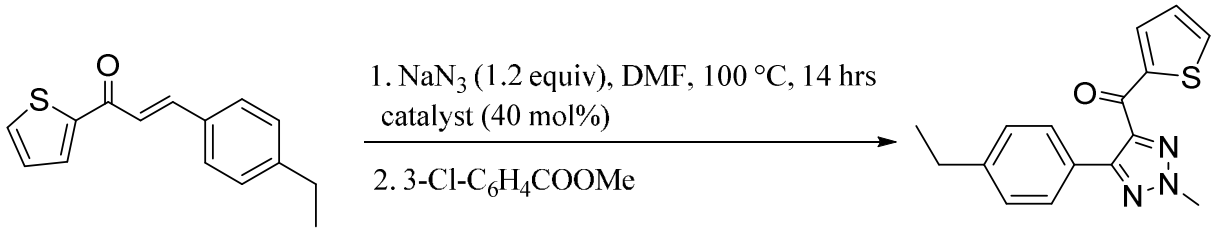
Entry	R	R^3	Yield (%) [b]	Product
1	CH_3	CH_2CH_3	---	---
2	C_6H_5	CH_3	77	2k
3	C_6H_5	CH_2CH_3	60	2n
4	C_6H_5	isopropyl	52	2o
5	C_6H_5	*t*-butyl	49	2p
6	C_6H_5	n-butyl	46	2q
7	C_6H_5	isoamyl	45	2s

[a]1h (1 mmol), NaN_3 (1.2 mmol), 40 mol % of ZrO_2-Cu_2-β-CD (50 mg, 0.036 mmol) in DMF (3 mL) at 100 °C in air for 14 hrs first then ester (1 mmol), was added to mixture and the reaction continued for 16-48 h. [b]Isolated yields.

Then we converged our interest to screen the reaction using different catalysts such as CuO, $CuSO_4$, α-Fe_3O_4, ZrO_2-β-CD, Cu_2-β-CD, and ZrO_2-Cu_2-β-CD (Table 2, entries 1-15). Among all, ZrO_2-Cu_2-β-CD was found to be very effective for the formation of N-2-alkylated product. CuO, $CuSO_4$, α-Fe_3O_4 gave only triazole anion without undergoing N-alkylation. $CuSO_4$ and Cu_2-β-CD gave mixture of products with low yields (Table 2, entries 2, 5). Then we screened the

reaction using ZrO_2-Cu_2-β-CD as a catalyst with different solvents such as DMF, DMSO, EtOH, THF, among them DMF was proved to be better solvent for the formation of N-2-alkylated triazoles (Table 2, entry 9) at 100 °C.

Table 2 Effect of catalyst and solvent on the reaction.



1h **2k**

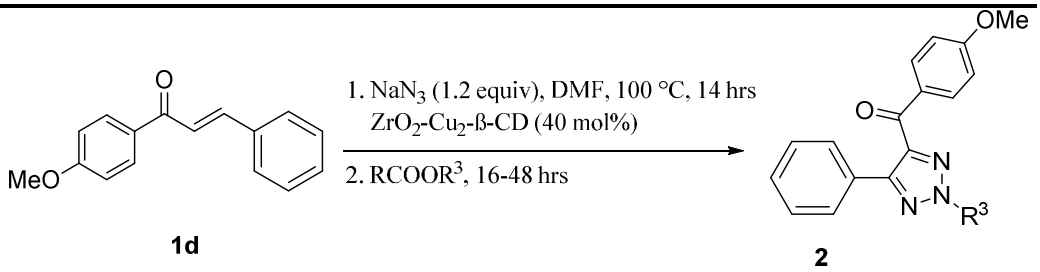
Entry	Catalyst	Temp(°C)	Mol%	Solvent	Time(h)	Yield(%)[b]
1	-----	125	---	DMF	24	---
2	CuO	125	10	DMF	18	50
3	$CuSO_4$	100	40	DMF	20	25
4	α-Fe_3O_4	120	10	DMSO	20	50
5	ZrO_2-β-CD	100	40	DMF	16	35
6	Cu_2-β-CD	100	40	DMF	20	30
7	ZrO_2-Cu_2-β-CD	75	10	DMF	16	58
8	ZrO_2-Cu_2-β-CD	100	20	DMF	13	72
9	**ZrO_2-Cu_2-β-CD**	**100**	**40**	**DMF**	**14**	**77**
10	ZrO_2-Cu_2-β-CD	120	40	DMF	14	55
11	CuO	100	40	DMF	12	67
12	ZrO_2-Cu_2-β-CD	100	20	EtOH	13	none
13	ZrO_2-Cu_2-β-CD	100	20	THF	13	none
14	ZrO_2-Cu_2-β-CD	75	40	DMF	20	55
15	CuO	100	20	DMF	16	50

[a] **1h** (1 mmol), NaN_3 (1.2 mmol), 40 mol % of ZrO_2-Cu_2-β-CD (50 mg, 0.036 mmol) in DMF (3 mL) at 100 °C in air for 14 hrs first, then 3-Cl-$C_6H_4COOCH_3$ (1 mmol), was added to mixture and the reaction continued for 16-48 h. [b] Isolated yields.

With the optimized reaction condition in hand, we next explored the generality and scope of the protocol using several substituted aryl alkyl esters (Table 3). The reaction of 2,4,5 tri substituted 1,2,3 triazole anion with esters containing chlorine atom at m-position of the aryl group goes

smoothly and regioselectively produced the corresponding 2, 4, 5-trisubstituted 1, 2, 3-triazoles with excellent yields (Table 3, entry 8). With Methyl benzoate as an alkylating agent, the moderate yield of desired product is observed (Table 3, entry 2) and the reaction with ethylbromoacetate yields the expected product in good yield (Table 3, entry 3). When we carried out the reaction with different alkyl benzoates containing halogens at different position produced corresponding 2, 4, 5-trisubstituted 1, 2, 3-triazoles with low yield (Table 3, entries 4-12). Disappointingly, 2-chloroethyl 3-chlorobenzoate did not promote the reaction (table 3, entry 12).

Table 3 Effect of different halogen substituents for the synthesis of triazoles.



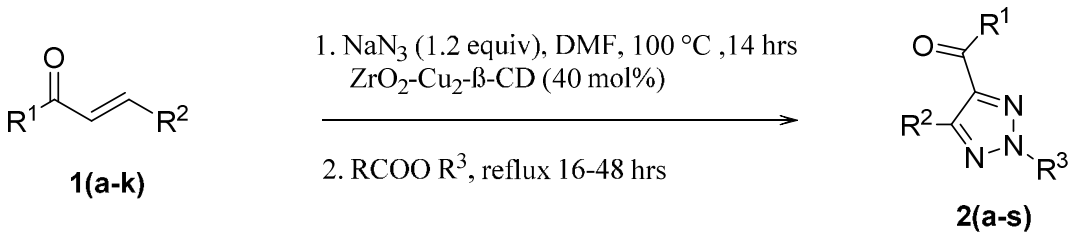
1d **2**

Entry	R	R^3	Yield(%) [b]	Product
1	CH_3	CH_2CH_3	---	---
2	C_6H_5	CH_3	63	2m
3	$BrCH_2$	CH_2CH_3	78	2m
4	2-BrC_6H_4	CH_3	53	2d
5	2-IC_6H_4	CH_3	trace	2d
6	2-FC_6H_4	CH_3	44	2d
7	2-ClC_6H_4	CH_3	60	2d
8	**3-ClC_6H_4**	**CH_3**	**81**	**2d**
9	4-ClC_6H_4	CH_3	57	2d
10	2,4-ClC_6H_4	CH_3	58	2d
11	3-ClC_6H_4	CH_2CH_3	68	2m
12	3-ClC_6H_4	CH_2CH_2Cl	-	-

[a] **1d** (1 mmol), NaN_3 (1.2 mmol), 40 mol % of ZrO_2-Cu_2-β-CD (50 mg, 0.036 mmol) in DMF (3 mL) at 100 °C in air for 14 hrs first, then ester (1 mmol), was added to mixture and the reaction continued for 16-48 h. [b] Isolated yields.

Furthermore, varieties of chalcones were used to investigate the substrate scope of the reaction as shown in Table 4. Generally, chalcones with electron-withdrawing substituents on R^1 and/or R^2 led to higher yields (Table 4, entries 1-3, 6-12, 14-18 and 20). In contrast, chalcones bearing a thiophene ring gave moderate yields (Table 4, entries 1-3, 7-11, 14-18 and 20). When we used methyl 3-chlorobenzoate reaction underwent substitution at faster rate and we observed moderate to good yields (Table 4, entry 1-7, 9-12, 14). With increasing alkyl chain length, as isopropyl, t-butyl, isoamyl aromatic esters, reactions proceeds slowly with lower yields of desired products (Table 4, entries 16-18, 20). When isopropyl 3-chlorobenzoate and phenyl 2,4-dichlorobenzoate were explored, only the trace of desired alkylated products were isolated.

Table 4 Substrate scope of different chalcones and esters.



R^1 = 2-thiophenyl, aryl;
R^2 = benzo[1,3]dioxole , aryl ;
R^3 = aryl, alkyl;

Entry	R^1	R^2	R^3	R	Time(h) [b]	Yield(%) [c]	Product
1	2-thiophenyl	4- $OCH_3C_6H_4$	CH_3	3-ClC_6H_4	16	80	**2a**
2	2-thiophenyl	3,4-$(OCH_3)_2$ C_6H_3	CH_3	3-ClC_6H_4	15	82	**2b**
3	2-thiophenyl	C_6H_5	CH_3	3-ClC_6H_4	16	76	**2c**
4	4-$OCH_3C_6H_4$	C_6H_5	CH_3	3-ClC_6H_4	14	81	**2d**
5	4-$OCH_3C_6H_4$	4-$CH_3C_6H_4$	CH_3	3-ClC_6H_4	15	82	**2e**
6	4-$OCH_3C_6H_4$	4-FC_6H_4	CH_3	3-ClC_6H_4	17	78	**2f**
7	2-thiophenyl	4-FC_6H_4	CH_3	3-ClC_6H_4	18	72	**2g**
8	2-thiophenyl	4-ethylC_6H_4	CH_2CH_3	Br CH_2	12	79	**2h**
9	2-thiophenyl	3,4,5-$(OCH_3)_3$ C_6H_2	CH_3	3-ClC_6H_4	14	81	**2i**
10	2-thiophenyl	benzo[1,3]dioxole	CH_3	3-ClC_6H_4	16	75	**2j**
11	2-thiophenyl	4-ethylC_6H_4	CH_3	3-ClC_6H_4	17	77	**2k**

12	4-$OCH_3C_6H_4$	4-BrC_6H_4	CH_3	3-ClC_6H_4	16	79	**2l**
13	4-$OCH_3C_6H_4$	C_6H_5	CH_2CH_3	3-ClC_6H_4	22	68	**2m**
14	2-thiophenyl	4-FC_6H_4	CH_3	C_6H_5	21	62	**2g**
15	2-thiophenyl	4-ethylC_6H_4	CH_2CH_3	3-ClC_6H_4	26	60	**2n**
16	2-thiophenyl	4-ethylC_6H_4	isopropyl	3-ClC_6H_4	30	Trace	**2o**
17	2-thiophenyl	4-ethylC_6H_4	*t*-butyl	3-ClC_6H_4	36	49	**2p**
18	2-thiophenyl	4-ethylC_6H_4	n-butyl	3-ClC_6H_4	32	46	**2q**
19	4-$OCH_3C_6H_4$	C_6H_5	C_6H_5	2,4 diClC_6H_4	48	Trace	**2r**
20	2-thiophenyl	4-ethylC_6H_4	isoamyl	3-ClC_6H_4	34	45	**2s**

[a] Chalcone (1 mmol), NaN_3 (1.2 mmol), 40 mol % of ZrO_2-Cu_2-β-CD (50 mg, 0.036 mmol) in DMF (3 mL) at 100 °C in air for 14 hrs first, then ester (1 mmol), was added to mixture and the reaction continued for 16-48 h. [b] Isolated yields.

Finally, confirmation of the structure and the site of N-alkylation of the product were obtained by the single crystal X-ray analysis of **2b** is shown in Figure 3. The reusability of the ZrO_2-supported Cu (II)-β-cyclodextrin nanoparticles has been studied. The ZrO_2-supported Cu (II)-β-cyclodextrin nanoparticles were collected by a filteration and washed four times with deionized water followed by methanol, dried in air and reused for the one-pot preparation of N-2-substituted1, 2, 3-triazoles from chalcones. We haven't found noticeable decrease in catalytic activity even after four catalytic cycles (Table 5).

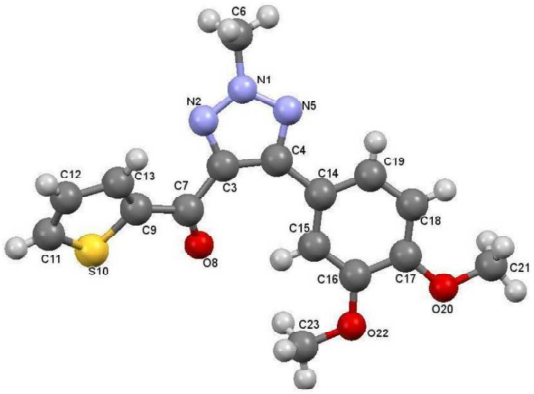


Fig. 3 Single crystal XRD pattern of **2b** with 50% probability**.**

Table 5 Recyclability test of ZrO_2 - supported Cu (ll) - β-cyclodextrin

Recycles	Catalyst recovery (wt%)	**Yield of 2a** (%)
1	90	81
2	88	79
3	87	77
4	85	74

Conclusion

we have developed an efficient ZrO_2 nanoparticles-supported Cu (II) - β-cyclodextrin complex catalyzed protocol for regioselective synthesis of N-2-alkylated 1,2,3-triazoles in excellent yield from chalcones via cycloaddition and post-triazole alkylation using different aryl-alkyl esters without any additives has been achieved for the first time. The regeneration of ZrO_2 nanoparticles-supported Cu (II) - β-cyclodextrin complex in situ by air oxidation is the advantage of our protocol and it reduces the catalyst load and increases the efficiency. The catalyst were collected easily by filtration and the reusability of the prepared nanocatalyst was successfully examined for four runs and found that it is effective up to four cycles with only a very slight loss of catalytic activity. This new, efficient protocol offers several advantages over many of the previously published procedures. Interestingly, this method could be highly useful to synthetic as well as medicinal chemists for the regioselective derivation of a variety of N-2-substituted-1,2,3-triazole derivatives. Scope of this novel catalyst being undertaken for the synthesis of other nitrogen containing heterocycles, in our research group.

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References:

1. H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem*., *Int. Ed*., 2001, **40**, 2004.
2. (*a*) R. A. Sheldon, I.Arends, U. Hanefeld, *Green Chemistry and Catalysis*., Wiley-VCH,Weinheim, 2007; (*b*) R. A. Sheldon, *Chem. Commun.*, 2008, **29**, 3352–3365; (*c*) P. Anastas, N. Eghbali, *Chem. Soc. Rev.*, 2010, **39**, 301.
3. S. Tan, X. Li, Y. Guo, Z. Zhang, *Nanoscale*., 2013, **5**, 860.
4. K. T. Yong, I. Roy, M. T. Swihart, P. N. Prasad, *J. Mater. Chem*., 2009, **19**, 4655.
5. P. Song, D. Wen, Z. X. Guo, T. Korakianitis, *Phys. Chem. Chem. Phys*, 2008, **10**, 5057.
6. H. Y. Shi, B. Deng, S. L. Zhong, L. Wang, A. W. Xu, *J. Mater. Chem.,* 2011, **21**, 12309.
7. (a) Y. Ding, Y. Wang, L. Zhang, H. Zhang, C. M. Li, Y. Lei, *Nanoscale.*, 2011, **3**, 1149; (b) O. A. Sadik, A. L. Zhou, S. Kikandi, N. Du, Q. Wang, K. Varner, *J. Environ. Monit*, 2009, **11**, 1782; (c) X. D. Wang, O. S. Wolfbeis, J. Robert, Meier*, Chem. Soc. Rev*., 2013, **42**, 7834.
8. D. Jariwala, V. K. Sangwan, L. J. Lauhon, T. J. Marks, M. C. Hersam, *Chem. Soc. Rev.,* 2013, **42**, 2824.
9. J. Liao, Z. Yang, H. Wu, D. Yan, et.al, *J. Mater. Chem. C.* 2013, **1**, 6541.
10. H. Kang, Y. Zhu, X. Yang, J. Shen, C. Chen, C. Li, *New J. Chem.*, 2010, **34**, 2166.
11. R. Narayanan, M. A. El-Sayed, *J. Phys. Chem. B.*, 2005, **109**, 12663.
12. (a) M. Whiting, J. Muldoon, Y.-C. Lin, S. M. Silverman,W. Lindstrom, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharpless, J. H. Elder, V. V. Fokin, *Angew. Chem.,Int. Ed.*, 2006, **45**, 1435; (b) H. C. Kolb, K. B. Sharpless, *Drug Discovery Today.*, 2003, **8**, 1128. (c) M. J. Giffin, H. Heaslet, A. Brik, Y. C. Lin, G. Cauvi, C.-H. Wong, D. E. McRee, J. H. Elder, C. D. Stout, B. E. Torbett, *J. Med. Chem*., 2008, **51**, 6263. (d) W.-Q. Fann, A. R. Katritzky, *in Comprehensive Heterocyclic Chemistry II,ed*. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, *Elsevier Science, Oxford.*, 1996, **4**, 1.
13. R. Huisgen, In *1,3-Dipolar Cycloaddition Chemistry*, Padwa, A., Ed, Wiley: New York, 1984.

14. (a) C. Z. Tao, X. Cui, J. Li, A. X. Liu, L. Liu, Q. X. Guo, *Tetrahedron Letters.*, 2007, **48**, 3525; (b) C. Zhang, B. Huang, Y. Chen, D. M. Cui, *New J. Chem.*, 2013, **37**, 2606; (c) S. Mohammed, A. K. Padala, B. A. Dar, B. Singh, B. Sreedhar, R. A. Vishwakarma, S. B. Bharate, *Tetrahedron.*, 2012, **68**, 8156; (d) N. V. Dubrovina, L. Domke, I. A. Shuklov, A. Spannenberg, R. Franke, A. Villinger, A. Börner, *Tetrahedron.*, 2013, **69**, 8809; (e) B. Kaboudin, Y. Abedi, T. Yokomatsu, *Org. Biomol. Chem*., 2012, **10**, 4543; (f) B. Kaboudin, R. Mostafalu, T. Yokomatsu, *Green Chem*., 2013, **15**, 2266; (g) S. Roy, T. Chatterjee, Sk. Manirul Islam, *Green Chem.,* 2013, **15**, 2532; (h) F. Alonso, Y. Moglie, G. Radivoy, M. Yus, *Org. Biomol. Chem*., 2011, **9**, 6385; (i) N. Mukherjee, S. Ahammed, S. Bhadra, B. C. Ranu, *Green Chem*., 2013, **15**, 389; (j) P. Abdulkin, Y. Moglie, B. R. Knappett, D. A. Jefferson, M. Yus, F. Alonso, A. E. H. Wheatley, *Nanoscale.*, 2013, **5**, 342; (k) P. Veerakumar, M. Velayudham, K. L. Lu, S. Rajagopal, *Catal. Sci. Technol*., 2011, **1**, 1512.

15. Selective methods of synthesizing N-1 substitued 1,2,3 triazoles: (a) C. W. Tornoe, C. Christensen, M. Meldal, *J. Org. Chem.,* 2002, **67**, 3057; (b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem., Int. Ed.,* 2002, **41**, 2596; (c) D. Yang, N. Fu, Z. Liu, Y. Li, B. Chen, *Synlett.,* 2007, **278**; (d) M. M. Majireck, S. Weinreb, *J. Org. Chem.,* 2006, **71**, 8680; (e) C. Spiteri, J. E. Moses, *Angew. Chem., Int. Ed.,* 2010, **49**, 31; (f) F. Shi, J. P. Waldo, Y. Chen, R. C. Larock, *Org. Lett.,* 2008, **10**, 2409; (g) V. Aucagne, D. A. Leigh, *Org. Lett.,* 2006, **8**, 4505; (h) B. Sreedhar, P. S. Reddy, V. R. Krishna, *Tetrahedron Lett.,* 2007, **48**, 5831; (i) W. Qian, D. Winternheimer, Allen, *J. Org. Lett*., 2011, **13**, 1682.

16. Methods of regioselectively synthesizing N-2 substitued 1,2,3 triazoles: (a) S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, *J. Am. Chem. Soc*., 2003, **125**, 7786; (b) Y. Chen, Y. Liu, J. L. Petersena, X. Shi, *Chem. Commun*., 2008, **28**, 3254; (c) J. Kalisiak, K. B. Sharpless, V. V. Fokin, *Org. Lett.,* 2008, **10**, 3171; (d) Y. Liu, W. Yan, Y. Chen, J. L. Petersen, X. Shi, *Org. Lett.,* 2008, **10**, 5389; (e) X. Wang, L. Zhang, H. Lee, N. Haddad, D. Krishnamurthy, C. H. Senanayake, *Org. Lett.,* 2009, **11**, 5026; (f) X. J. Wang, L. Zhang, D. Krishnamurthy, C. H. Senanayake, P. Wipf, Org. Lett., 2010, **12**, 4632; (g) L. Zhang, Z. B. Li, X. J. Wang, N. Yee, C. H. Senanayske, *Synlett.,* 2012, **23**, 1052; (h) Murali, M.G, Tharmalingam, P, *J. Org. Chem.,* 2012, **77**, 5063; (i) K. S. Mariola, M. P. Ewa, R. Tomasz, *Tetrahedron.,* 2012, **68**, 214–225; (j) W. M. Yan, T. Liao, O. Tuguldur, C. Zhong, J. L. Petersen, X. D. Shi, *Chem.–Asian J*., 2011, **6**, 2720; (k) Ahmed Kamal, Ponnampalli Swapna, *RSC Advances.,* 2013, **3**, 7419.

17. K. S. Balachandran, I. Hiryakkanavar, M. V. George, *Tetrahedron.,* 1975, **31**, 1171.

18. X. Liu, X. Li, Y. Chen, D. Wang, J. Chen, B. Chen, *Asian J. Org. Chem*., 2013, **2**, 212.

19. J. Li, Y. Zhang, D. Wang, W. Wang, T. Gao, L. Wang, J. Li,G. Huang, B. Chen, *Synlett.*, 2010, 1622.

20. Y. Zhang, X. Li, J. Li, J. Chen, X. Meng, M. Zhao, B. Chen, *Org. Lett*., 2012, **14**, 26.

21. X. Liu, J. Li., *New J. Chem.,* 2013, **37**, 965.

22. S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, *J. Am. Chem. Soc.*, 2002, **125**, 7786.

23. M. Koszytkowska-Stawinska, E. Mironiuk-Puchalska, T. Rowicki, *Tetrahedron*., 2012, **68**, 214.

24. Y. Matsui, T. Kurita, Y. Date, *Bull. Chem. Soc. Jpn.* 1972, **45**, 3229.

25. L. Bai, A. F. Wyrwalski, C. Machut, P. Roussel, E. Monflier, A. Ponchel, *Cryst Eng Comm.,* 2013, **15**, 2076.